PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/005601	18.03.2005	18.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/575, C12Q1/68

Applicant
SUCAMPO AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Meyer, W

Telephone No. +49 89 2399-8157

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. , 25-28, 34, 35

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. , 25-28, 34, 35

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-24, 29-33 (all partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-24, 29-33
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24, 29-33
Industrial applicability (IA)	Yes:	Claims	1-24, 29-33
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/JP2005/005601

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: BROWN MICHAEL D ET AL: "Phylogenetic analysis of Leber's hereditary optic neuropathy mitochondrial DNA's indicates multiple independent occurrences of the common mutations" HUMAN MUTATION, vol. 6, no. 4, 1995, pages 311-325, XP009054854 ISSN: 1059-7794

D2: HOLLANDER D A ET AL: "OUTFLOW PATHWAY ANOMALIES ASSOCIATED WITH MULTIPLE CYP1B1 MUTATIONS IN CONGENITAL GLAUCOMA" ARVO ANNUAL MEETING ABSTRACT SEARCH AND PROGRAM PLANNER, vol. 2003, 2003, page Abstract No. 1117, XP009054897 & ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY; FORT LAUDERDALE, FL, USA; MAY 04-08, 2003

D3: BU X ET AL: "X CHROMOSOME-LINKED AND MITOCHONDRIAL GENE CONTROL OF LEBER HEREDITARY OPTIC NEUROPATHY EVIDENCE FROM SEGREGATION ANALYSIS FOR DEPENDENCE ON X CHROMOSOME INACTIVATION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 88, no. 18, 1991, pages 8198-8202, XP002347836 ISSN: 0027-8424

D4: CHINNERY P F ET AL: "The mitochondrial ND6 gene is a hot spot for mutations that cause Leber's hereditary optic neuropathy" BRAIN, vol. 124, no. 1, January 2001 (2001-01), pages 209-218, XP002347837 ISSN: 0006-8950

D5: WO 02/22881 A (DZGENES, LLC; MOSKOWITZ, DAVID, W) 21 March 2002 (2002-03-21)

D6: WO 02/24747 A (EPIDAUROS BIOTECHNOLOGIE AG; BRINKMANN, ULRICH; HOFFMEYER, SVEN) 28 March 2002 (2002-03-28)

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-24 and 29-33 does not involve an inventive step in the sense of Article 33(3) PCT.
The document D5 is regarded as being the closest prior art and discloses (the references in parentheses applying to this document):
Document D5 discloses specific genetic polymorphism associated with optic

neuropathy associated with the expression of endothelin-1 promoter (D5, Abstract and Claims). The subject-matter of present claims therefore differs from this known D5 in that a specific mutation is presented.
The problem to be solved by the present invention may therefore be regarded as the provision of jet another mutation in associated with the expression of the Endothelin gene. The solution proposed in present claims of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) as a skilled person will automatically be lead to determine further mutations.

2. The applicant's attention is further drawn to Documents D2-D4. It appears that these documents are also prejudicial to the novelty and/or the inventive activity (or inventiveness) of the claimed subject-matter.

The document D1 discloses (D1, Abstract) specif genetic polymorphism associated with optic neuropathy (here LHON), or D2, discloses a strong association between optic neuropathy (here congenital glaucoma) and chromosome 2p21 encoding a cytochrome P4501B1 (see D2, Abstract) or D3, disclosing that LHON is not only mitochondrial but also X-chromosome linked (D3 Abstract) orv D4 discloses that not only in mitochondrial DNA (mtDNA) complex I, but also in NADH:ubiquinone oxireductatse (ND) genes (ND1, ND4 or ND6) (D4, Abstract),

Re Item IV

3. The present application does not comply with the requirements of unity of invention. 21 separate inventions have been identified. Each of them is characterised by an individual "special technical feature"; there is no technical interrelation between these inventions (see below). The applicants was therefore asked to pay additional search fees.

4. Rule 13(2) PCT demands that "Rule 13.1 PCT shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression 'special technical features' shall mean those technical features which define a contribution which each of the claimed invention considered as a whole makes over the prior art." This amounts to a requirement that this single general concept must be novel and inventive. The PCT

Preliminary Examination Guidelines C-III 7.6 state more precisely that "if the common matter of the independent claim is well known, and the remaining subject-matter differs without there being any unifying novel concept common to all of them, then clearly there is lack of unity".

5. The presently claimed subject-matter does not fulfil the necessary requirements on unity of invention as outlined above: In view of the disclosure of the present application, a technical problem to be solved is the determination of Single nucleotide polymorphisms (SNPs) being associated with optic neuropathy (compare page 7 line 7-10) of application.
The alleged common technical feature of all solutions to this problem is the provision of genetic polymorphism associated with optic neuropathy (see Claim 1).
The available prior art discloses at least one solution to the said technical problem; moreover, the prior art solution shows the above defined technical features: The prior art provide ample opportunities of genetic polymorphism associated with optic neuropathy. For example D1, (Brown Michael D; et al. 1995; Abstract) discloses specif genetic polymorphism associated with optic neuropathy (here LHON), or D2, discloses a strong association between optic neuropathy (here congenital glaucoma) and chromosome 2p21 encoding a cytochrome P4501B1 (see D2, Abstract) or D3, disclosing that LHON is not only mitochondrial but also X-chromosome linked (D3 Abstract) or D4 discloses that not only in mitochondrial DNA (mtDNA) complex I, but also in NADH:ubiquinone oxireductatse (ND) genes (ND1, ND4 or ND6) (D4, Abstract), D5 discloses single nucleotide polymorphism (SNPs) in endothelin-1 gene which is associated with various diseases (D5, claims and p 1 first paragraph), D6, discloses single nucleotide polymorphism (SNPs) which are provided for the genes encoding human endothelin 1 and 2 and 3, endothelin-converting enzyme, and endothelin receptors A and B (D6, Abstract and claims).

6. In consequence the solution in its general form as claimed to the problem posed in the present application is therefore not novel. It follows that there is no common special technical feature for the whole scope of the present application that would define an appreciable contribution (e.g. novel and/or non-trivial) over the prior art.

7. In view of the prior art (supra), the technical content of the present application has to be rearranged into 21 individual objective problems with independent solutions

(non-unity a posteriori):
- Problem 1: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 1: Provision of a polymorphism associated with expression of the Endothelin 1 gene (coding/non-coding)

- Problem 2: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 2: Provision of a polymorphism associated with expression of the Endothelin Receptor A (coding/non-coding)

- Problem 3: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 3: Provision of a polymorphism associated with expression of the Endothelin Receptor B (coding/non-coding)

- Problem 4: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 4: Provision of a polymorphism associated with the Mitochondrial gene

- Problem 5: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 5: Provision of a polymorphism associated with Angiotensin II type 1 receptor gene promoter region

- Problem 6: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 6: Provision of a polymorphism associated with Angiotensin II type 2 receptor gene promoter region

- Problem 7: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 7: Provision of a polymorphism associated with the Paraoxonase 1 gene I

- Problem 8: Provision of an alternative genetic polymorphism associated with optic

neuropathy
- Solution 8: Provision of a polymorphism associated with the Noelin 2 gene

- Problem 9: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 9: Provision of a polymorphism associated with the adrenergic receptor gene

- Problem 10: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 10: Provision of a polymorphism associated the Myocilin gene

- Problem 11: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 11: Provision of a polymorphism associated with Optineurin alone and combinations with the TNFalpha gene

- Problem 12: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 12: Provision of a polymorphism associated with expression of the E-Selectin gene

- Problem 13: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 13: Provision of a polymorphism associated the TP53 gene

- Problem 14: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 14: Provision of a polymorphism associated with the Microsomal epoxide hydrase I gene

- Problem 15: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 15: Provision of a polymorphism associated with Endothelin converting enzyme gene promoter region gene

- Problem 16: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 16: Provision of a polymorphism associated the Heatshock protein promoter region

- Problem 17: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 17: Provision of a polymorphism associated with CD95 gene promoter region gene

- Problem 18: Provision of an alternative genetic polymorphism associated with optic neuropathy
- Solution 18: Provision of a polymorphism associated with adrenergic receptor gene

- Problem 19: Provision of an isolated polynucleotide
- Solution 19: Provision of an isolated polynucleotide disclosed in claim 25

- Problem 20: Provision of an isolated polynucleotide
- Solution 20: Provision of an isolated polynucleotide disclosed in claim 27

- Problem 21: Provision of an isolated polynucleotide
- Solution 21: Provision of an isolated polynucleotide disclosed in claim 28

8. Please be advised that disclaimers may restore novelty, but not an inventive step and a common inventive concept.

9. Please note also that Rule 13 PCT has a regulatory function (to prevent unjustified saving of fees, and to ensure ready comprehensibility). Also from this more pragmatic approach the present application lacks unity of invention: First, due to the lack of constant characteristic "special technical features", competitors cannot inform themselves readily on the existing situation regarding protective rights. Second, the equitable levying of fees has to be respected. Because of its heterogeneous content, the present application entails a far greater than average expense in the procedure up to grant (keep in mind that there is an ample background concerning subject-matter with related technical and functional features, thus necessitating

several independent searches of restricted scope).